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Proposal of Toxicity Risk Index (TRI) for Warning Idiosyncratic Drug Toxicity

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Drug toxicity impedes not only its clinical use but also drug development. In the present study, a toxicity risk index (TRI), which is an index for warning idiosyncratic drug toxicity (IDT), was devised. The TRI of drugs was defined as a function of dose, pharmacokinetic parameters, and toxicokinetic data from covalent binding experiment. Twenty drugs classified into three categories by a report [1], were studied with TRI. The three categories were BBW (drugs with a block box warning for IDT), WNG (drugs without a black box warning but with a warning for IDT) and SAFE (drugs without any warning). The TRIs of drugs classified as SAFE were distinctly different from those classified as BBW. The TRI of SAFE drugs were lower than 0.456 (nmol/mg protein). In contrast, the TRI of the BBW drugs were higher than 1.10 (nmol/mg protein). These results warned us that a drug candidate, where the TRI is higher than 1.0 nmol/mg protein, should be categorized as a BBW drug. Thus, TRI may be useful for decision-making in drug development and its clinical use, and is proposed for warning IDT. Further study is now going on for obtaining a cut-off value with a statistical meaning.

[1] Nakayama, S., Atsumi, R., Takakusa, H., Kobayashi, Y., Kurihara, A., Nagai, Y., Nakai, D., Okazaki, O., A zone classification system for risk assessment of idiosyncratic drug toxicity using daily dose and covalent binding, *Drug Metabolism and Disposition*, 37: 1970-1977, 2009.